Cancer cells acquire a drug resistant, highly tumorigenic, cancer stem-like phenotype through modulation of the PI3K/Akt/beta-catenin/CBP pathway.

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Public Summary:
Cancer initiation and progression have been attributed to newly discovered subpopulations of self-renewing, highly tumorigenic, drug-resistant tumor cells termed cancer stem cells. Recently, we and others reported a new phenotypic plasticity wherein highly tumorigenic, drug-resistant cell populations could arise not only from pre-existing cancer stem-like populations but also from cancer cells lacking these properties. In the current study, we hypothesized that this newfound phenotypic plasticity may be mediated by PI3K/Akt and Wnt/β-catenin signaling, pathways previously implicated in carcinogenesis, pluripotency and drug resistance. These studies provide a mechanistic model wherein PI3K/Akt/beta-catenin/CBP signaling mediates phenotypic plasticity in and out of a drug-resistant, highly tumorigenic state. Therefore, targeting this pathway has unique potential for overcoming the therapy resistance and disease progression attributed to the cancer stem-like phenotype.

Scientific Abstract:
Cancer initiation and progression have been attributed to newly discovered subpopulations of self-renewing, highly tumorigenic, drug-resistant tumor cells termed cancer stem cells. Recently, we and others reported a new phenotypic plasticity wherein highly tumorigenic, drug-resistant cell populations could arise not only from pre-existing cancer stem-like populations but also from cancer cells lacking these properties. In the current study, we hypothesized that this newfound phenotypic plasticity may be mediated by PI3K/Akt and Wnt/beta-catenin signaling, pathways previously implicated in carcinogenesis, pluripotency and drug resistance. Using GFP expression, Hoechst dye exclusion and fluorescence activated cell sorting (FACS) of cancer cell lines, we identified and tracked cancer stem-like side populations (SP) of cancer cells characterized by high tumorigenicity and drug resistance. We found that pharmacological inhibition or genetic depletion of PI3K and AKT markedly reduced the spontaneous conversion of nonside population (NSP) cells into cancer stem-like SP cells, whereas PI3K/Akt activation conversely enhanced NSP to SP conversion. PI3K/AKT signaling was mediated through downstream phosphorylation of GSK3beta, which led to activation and accumulation of beta-catenin. Accordingly, pharmacological or genetic perturbation of GSK3beta or beta-catenin dramatically impacted conversion of NSP to SP. Further downstream, beta-catenin's effects on NSP-SP equilibrium were dependent upon its interaction with CBP, a KAT3 family coactivator. These studies provide a mechanistic model wherein PI3K/Akt/beta-catenin/CBP signaling mediates phenotypic plasticity in and out of a drug-resistant, highly tumorigenic state. Therefore, targeting this pathway has unique potential for overcoming the therapy resistance and disease progression attributed to the cancer stem-like phenotype.